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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,872	BAO ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

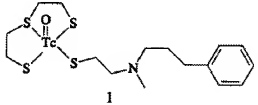
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/21/04, 7/27/05, 11/10/05, 7/10/07.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 6/26/2009 is acknowledged. The traversal is on the ground(s) that a special technical feature has been shown in the claims because WO 96/30054 does not disclose Applicant's claimed invention of claims 1-41. Applicant asserts that WO 96/30054 defines a carbonylated metal (1) with oxygenated ligands (L), and that the chemistry of a carbonylated metal is different than that of the claimed invention and requires the use of oxygentated ligands (L) in order to stabilize the metal chelate. Applicant contends that WO 96/30054 does not refer to alternative ligand substitutes, and that Groups II, III, and IV of the restriction define non-obvious changes to an oxo metal core and not a carbonylated metal core, and that SXS ligands are claimed by Applicant. This is not found persuasive. The WO 96/30054 document is not limited to carbonylated metal complexes. For example, structures such as the following are disclosed (see abstract, pages 5-9), which read on a compound of formula 1 in the instant claims:



1

Therefore, the "common" feature in Groups 1-VI set forth in the restriction requirement (i.e. a compound of formula 1) is not novel, and thus the "common" feature

cannot be a "special technical feature" under PCT Rule 13.2, and thus lack of unity has been established. The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-41 are pending, of which claims 1-11 and 23-41 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 12-22 are readable upon the elected invention and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

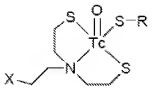
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Permettis *et al.* (*J. Med. Chem.*, 1997, 90(160), p. 2539-46), in view of Phillips (US

5,143,713), further in view of Gupta *et al.* (Radiochimica Acta, 2001, 89(1), p. 43 (abstract).

Permettis discloses a series of neutral, lipophilic ^{99m}Tc mixed-ligand complexes of the general formula 99mTcOL^{1}L^2, where L^{1}H$_2$ is an N-substituted bis-(2-mercaptoethyl)amine, [X-$CH_2CH_2N(CH_2CH_2SH)_2$], [SNS], and L^{2}H is a monodentate thiol (RSH), [S], which were synthesized and evaluated in rodents for potential use in brain blood flow imaging. Structure-activity relationships of novel ^{99m}Tc(V)O SNS/S complexes in mice are reported and discussed. Selected complexes were further studied in rats. High brain uptake, comparable to that of 99mTc-*d,l*-HMPAO, and sufficient retention 60 min postinjection were provided with complex **18** [X = $(C_2H_5)_2N$ and R = *p*-$CH_3OC_6H_4CH_2$] (see abstract). Selected compounds are disclosed as in Table 1.



compd	X	R	MW	log PC
1	H	*p*-$CH_3OC_6H_4$	417.49	2.77
2	CH_3O	*p*-$CH_3OC_6H_4$	447.52	2.81
3	$(CH_3)_2N$	*p*-$CH_3OC_6H_4$	460.56	2.38
4	$(C_2H_5)_2N$	*p*-$CH_3OC_6H_4$	488.61	2.63
4a	$(C_2H_5)_2N$	*p*-$CH_3OC_6H_4$	488.61	2.54
5	$(C_2H_5)_2N$	*m*-$CH_3OC_6H_4$	488.61	2.58
6	$(C_2H_5)_2N$	*o*-$CH_3OC_6H_4$	488.61	2.60
7	$(C_2H_5)_2N$	C_6H_5	458.59	2.63
8	$(C_2H_5)_2N$	*p*-BrC_6H_4	537.49	2.87
9	$(C_2H_5)_2N$	*p*-IC_6H_4	548.48	2.77
10	$(C_2H_5)_2N$	*p*-$CH_3C_6H_4$	472.61	2.66
11	$(C_2H_5)_2N$	*p*-$C_2H_5C_6H_4$	486.64	2.70
12	$(C_2H_5)_2N$	*p*-*i*-$C_3H_7C_6H_4$	500.67	2.83
13	$(C_2H_5)_2N$	*p*-*n*-$C_4H_9C_6H_4$	514.69	2.99
14	$(C_2H_5)_2N$	*p*-*t*-$C_4H_9C_6H_4$	514.69	2.97
15	$(C_2H_5)_2N$	3,4-$(CH_3)_2C_6H_3$	486.64	2.65
16	$(C_2H_5)_2N$	1-naphthyl	508.65	2.66
17	$(C_2H_5)_2N$	benzyl	472.61	2.38
18	$(C_2H_5)_2N$	*p*-$CH_3OC_6H_4CH_2$	502.64	2.61
19	$(C_2H_5)_2N$	*p*-*t*-$C_4H_9C_6H_4CH_2$	528.72	2.53
20	CH_3O	benzyl	431.52	2.66

Permettis does not disclose incorporation of ^{99m}Tc(V)O SNS/S complexes into liposome.

Phillips discloses stable ^{99m}Tc-labeled liposomes and their novel methods of preparation. The method of preparation results in over 95% labeling efficiency and produces labeled liposomes that are surprisingly stable in vivo for relatively long periods of time. The labeled liposomes are excellent imaging agents. Labeled

liposomes (LL) may be prepared by incubating liposomes with a label, generally a radionuclide, in the form of a complex which acts as a carrier for the label (column 4, lines 55+). It has been found that labeling is surprisingly efficient when the incubating is performed in the presence of an antioxidant compound. The antioxidant compound may be present in the incubation mixture of labeled carrier and liposomes, but is most preferably incorporated within the liposome prior to incubation with the label carrier. It was discovered that labeling is highly efficient when an antioxidant is encapsulated within preformed liposomes or liposome-encapsulated protein. Liposomes to be labeled may be first incubated with the antioxidant. This antioxidant/liposome mixture may then be washed, removing excess antioxidant not attached to the liposome surface. These prepared liposomes may then be incubated with the labeled carrier. Although the antioxidant may be added to the incubation mixture with liposomes or liposome-encapsulated protein, washed and then added to the label carrier, this procedure provides liposomal preparations that are less stable in vivo. This is so even though the initial labeling efficiency is quite high. Most preferably the antioxidant compound is an inorganic or organic reducing agent, for example Sn^{+2} or glutathione. Compounds with free sulfhydryl appear to be suitable, for example, cysteine. It is possible, at least in the case of a ^{99m}Tc-HMPAO, that presence of a reducing agent converts lipophilic ^{99m}Tc-HMPAO to a hydrophilic form that becomes trapped inside the liposome (column 5, lines 37+). A preferred carrier will depend to some extent on the lipid composition and surface charge of the liposome which can be positive, negative or neutral. A preferred carrier is HMPAO. This carrier readily crosses the membrane of

negatively charged liposomes. Other carriers could be chosen on their ability to complex with the selected radionuclide and the efficiency of transport across the liposomal membrane to mediate exchange with the encapsulated capture material (column 7, lines 9-18). Liposome components include distearoyl phosphatidylcholine (DSPC), cholesterol, etc. (Example 1). Regarding claim 21, Figure 7 shows ^{99m}Tc radioactive counts of capillaries drawn serially after infusion of 25 milliliters of ^{99m}Tc-labeled LEH at a concentration of 50 mg total lipid per milliliter into a 2 killgram New Zealand rabbit. See also Examples 2-4. Regarding claim 22, Phillips teaches that ^{99m}Tc liposomes also have potential in assessing the effectiveness of targeting with liposomes having antibodies attached to the surface. Antibodies to infectious agents or to tumor cells would bind to the targeted areas allowing radioimaging and possible delivery of drugs to the site (column 10, lines 31-36).

Gupta discloses the reactivity of ^{99m}Tc(V) "3+1" mixed-ligand complexes towards glutathione, the complexes undergo transchelation reactions with glutathione.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute a SNS/S ^{99m}Tc carrier ligand as a functional equivalent to HMPAO as a ^{99m}Tc carrier in the methods disclosed by Phillips. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to

supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (SNS/S and HMPAO) and their functions were known in the art at the time of the instant invention as ^{99m}Tc carrier ligands. For example, Permettis teaches ^{99m}Tc(V)O SNS/S complexes displaying high brain uptake, comparable to that of ^{99m}Tc-*d,l*-HMPAO (abstract). One of ordinary skill in the art could have substituted one known ^{99m}Tc carrier for another in the methods of Phillips, and the results of the substitution would have been predictable, that is successful incorporation of ^{99m}Tc via a carrier ligand into liposome for scintigraphic imaging. One would have had a reasonable expectation of success in doing so because Permettis teaches that his chelators are neutral and lipophilic (abstract), and Phillips teaches that in the case of ^{99m}Tc-HMPAO, that presence of a reducing agent (glutathione) converts lipophilic ^{99m}Tc-HMPAO to a hydrophilic form that becomes trapped inside the liposome. Since Gupta teaches that ^{99m}Tc(V) "3+1" mixed-ligand complexes undergo transchelation reactions with glutathione, which one would expect the lipophilic ^{99m}Tc(V)O SNS/S complex would be capable of crossing the phosphlipid membrane and would then be rendered upon exposure to glutathione lipophilic such as to become trapped within liposome, and thus one of ordinary skill would expect similar uptake of ^{99m}Tc SNS/S complexes into liposome as was observed for ^{99m}Tc HMPAO complexes.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS